by elevated amounts of a hormone); page 9, lines 16-17 (disease caused by abnormal glycosylation); page 4, lines 10-20, and page 5, line 1 (molecule is a polypeptide); page 6, lines 26-30 (higher level of polypeptide as compared to non-diseased cells); page 17, lines 14-18 and page 18, lines 5-23 (specific normal cellular proteins expressed at abnormally high levels). Claims 5 and 6 were amended to properly depend from claim 1. Claim 27 was amended to properly characterize and limit the claimed Markush group and should therefore be examined. A copy of all of the pending claims as they are believed to have been amended is attached to this Amendment as an appendix.

The present invention is directed to the surprisingly useful method of treating diseases wherein the cells to be killed express an abnormally elevated level of a polypeptide compared to normal cells, or an infectious agent protein.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-4, 14-18, 25-26, and 28-29 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

Claim 1 has been amended to define the disease to be treated. The disease is characterized by an abnormally elevated amount of a polypeptide as compared to the non-diseased state, or by expression of an infectious agent protein. The disease is selected from the group consisting of a cancer, a disease caused by a pathogen, a disease associated with abnormal

glycosylation of polypeptides, and a disease associated with abnormally elevated amounts of a hormone. Claim 5 has been deleted from the pending claims.

One of ordinary skill in the art will clearly understand what is meant by an "abnormal peptide" in the context of the specific diseases mentioned. It is generally understood by those of ordinary skill in the art that CTL act by killing specific (i.e. "presenting") cells in the patient. CTLs target and kill specific cells. If they are administered to a patient they will kill specific cells within the patient to which they are targeted. Furthermore, their very name (*cytotoxic* T lymphocytes) indicates that they kill cells. Page 24, lines 15-19, describes the lysis or elimination (i.e. killing) of the target cell in a particular embodiment of the invention, and the Examples show killing of tumor cells in a mouse model. In particular, page 51, lines 12-14, specifically refers to the use of CTL to specifically *kill* leukaemic cells (the target cell). Additionally, please see the last sentence of page 58 which describes tumor *cell killing*.

The Examples show the killing of presenting tumor cells by CTL. For example, lines 26-5, bridging pages 51 and 52, show isolated CTL which are specific for the mdm 100 peptide presented by allogeneic H-2K^b class I molecules. *In vitro*, these CTL discriminate between transformed and normal cells, killing specifically K^b positive melanoma and lymphoma tumors (which present mdm 100) but not K^b-expressing dendritic cells. *In vivo*, the CTL showed anti-tumor activity and delayed the growth of melanoma as well as lymphoma tumors in H-2^b recipient mice. The Applicant respectfully submits that the claims, as amended, clearly define and limit the scope of the claimed method and are fully supported by the specification.

Rejection Under 35 U.S.C. § 112, second paragraph

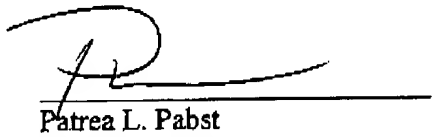
Claims 1-8, 14-18, 25-26, and 28-29 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Applicant has deleted the term abnormal "antigen" from claim 1 and inserted in its place an abnormally elevated amount of a "polypeptide". Base claim 1, as amended, clearly defines the metes and bounds of the claimed method directed to killing cells in a patient with the defined diseases characterized by an elevated amount of a polypeptide or by expression of an infectious agent protein. Clear support for an abnormally elevated amount of a polypeptide can be found, for example, at page 4, lines 10-20, and page 5, line 1 (molecule is a peptide); page 6, lines 26-30 (higher level of polypeptide as compared to non-diseased cells); page 17, lines 14-18 and page 18, lines 5-23 (specific normal cellular proteins expressed at abnormally high levels). The amended claims no longer refer to mutant polypeptides.

U.S.S.N. 09/101,413
Filed: August 7, 1998
AMENDMENT AND RESPONSE TO OFFICE ACTION

Allowance of claims 1-3, 5-18, and 25-29 is respectfully solicited.

Respectfully submitted,



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U.S.S.N. 09/101,413
Filed: August 7, 1998
MARKED UP VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

Marked Up Version of Amended Claims

Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (Four times amended) A method of killing cells in a patient with a disease selected from the group consisting of a cancer, a disease caused by a pathogen, a disease associated with abnormal glycosylation of polypeptides, and a disease associated with abnormally elevated amounts of a hormone; wherein the disease is characterized by expression [by the patient of an abnormal antigen or] of an abnormally elevated amount of a [antigen] polypeptide as compared to the non-diseased state, or by expression of an infectious agent protein, the method comprising

administering to the patient a therapeutically effective amount of cytotoxic T lymphocytes (CTL),

wherein the CTLs have a different HLA class I complex (or equivalent) than the cells to be killed, and

the CTLs specifically recognize a peptide portion of the [abnormal antigen or antigen] polypeptide which is abnormally elevated in patients with the disease or the infectious agent protein, when the peptide is presented by the HLA class I complex (or equivalent) on the surface of cells to be killed, wherein the HLA class I complex (or equivalent) type presenting the peptide in the cells to be killed is not present in the CTLs to be administered to the patient, and

the CTLs kill the presenting cells.

2. A method according to Claim 1 wherein the CTL are a clonal population of CTL.

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3. (Amended) A method according to Claim 1 wherein the CTL are substantially free of other cell types.

Please cancel claim 4.

5. (Twice amended) A method according to Claim [4] 1 wherein the polypeptide is a mutant polypeptide associated with the diseased cells.

6. (Twice amended) A method according to Claim [4] 1 wherein the polypeptide is present at an abnormally elevated amount in the diseased cells compared to non-diseased cells.

7. (Amended) A method according to Claim 1 wherein the disease is a cancer.

8. A method according to Claim 7 wherein the cancer is any one of breast cancer; bladder cancer; lung cancer; prostrate cancer; thyroid cancer; leukaemias and lymphomas such as CML, ALL, AML, PML; colon cancer; glioma; seminoma; liver cancer; pancreatic cancer; bladder cancer; renal cancer; cervical cancer; testicular cancer; head and neck cancer; ovarian cancer; neuroblastoma and melanoma.

9. (Amended) A method according to Claim 1 wherein the disease is caused by a chronic viral infection.

10. (amended) A method according to Claim 9 wherein the virus is selected from the group consisting of HIV, papilloma virus, Epstein-Barr virus, HTLV-1, hepatitis B virus, hepatitis C virus and herpes virus.

11. A method according to Claim 10 wherein the virus is HIV.

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12. (Amended) A method according to Claim 1 wherein the disease is associated with an abnormally elevated amount of a hormone.

13. (Amended) A method according to Claim 1 wherein the disease is a bacterial disease caused by a chronic bacterial infection.

14. (Amended) A method according to Claim 1 further comprising the step of determining the HLA class I (or equivalent) molecule type of the patient prior to administration of the CTL.

15. (Amended) A method according to Claim 14 wherein the type is determined using DNA typing.

16. (Amended) A method according to Claim 1 wherein the patient is human.

17. (Amended) A method according to Claim 14 wherein the cytotoxic T lymphocyte is selected from a library of CTL clones, the library comprising a plurality of CTL clones derived from individuals with differing HLA class I (or equivalent) molecule type and each CTL clone recognises the diseased cells.

18. (Amended) A method according to Claim 17 wherein each CTL clone recognises at least part of the same molecule contained in or associated with the diseased cells.

25. (Twice Amended) A method according to Claim 1 wherein the cells to be killed are selected from the group consisting of a cancer cell, a virus-infected cell, a bacterium infected cell and a cell expressing an abnormally elevated amount of a hormone.

26. (Twice Amended) A method according to Claim 1 wherein the patient is a human.

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Filed: August 7, 1998
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27. (Three times amended) A method according to Claim 1 wherein the [molecule] polypeptide is selected from the group consisting of cyclin D1, cyclin E, mdm 2, EGF-R, erb-B2, erb-B3, FGF-R, insulin-like growth factor receptor, Met, myc, and p53[, BCL-2, mutant p53, a polypeptide associated with the BCR/ABL translocation in CML and ALL, mutant CSF-1 receptor, mutant APC, mutant RET, mutant EGFR, a polypeptide associated with PML/RARA translocation in PML, a polypeptide associated with E2A-PBX1 translocation in pre B leukaemias and in childhood acute leukaemias, human papilloma virus proteins, Epstein-Barr virus proteins, HTLV-1 proteins, hepatitis B virus proteins, hepatitis C virus proteins, herpes-like virus proteins and HIV encoded proteins].

28. (Twice Amended) A method according to Claim 1 further comprising determining the HLA Class I (or equivalent) type of the healthy individual.

29. (Amended) A method according to Claim 28 wherein the HLA class I (or equivalent) type is determined by DNA analysis.